DEVICE GMP

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ORIGINAL

APPLICATIONS AND INTERPRETATIONS FOR THE FIELD INVESTIGATOR

U.S. Department of Health and Human Services
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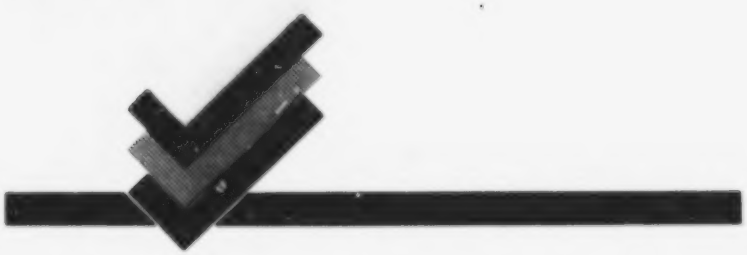
DEVICE GMP



APPLICATIONS AND INTERPRETATIONS FOR THE FIELD INVESTIGATOR

I

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INTRODUCTION

This booklet is the result of a compilation of questions received from members of the medical device industry and from FDA field personnel about specific interpretations and practical applications of the Device GMP.

Answers were provided by the Division of Compliance Programs, Office of Compliance, Bureau of Medical Devices, in consultation with other Bureau and Agency offices.

This information has been compiled for distribution to the field as part of BMD's effort to assure accuracy and consistency in the application and interpretation of the GMP rule.

The booklet will be updated periodically to reflect further GMP applications and interpretations as they are added to the body of established procedures.

Field personnel are invited to direct their requests for information, as well as their suggestions and reactions, to:

GMP Section
Industry Programs Branch, HFK-132
Division of Compliance Programs
(301) 427-7194.

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SUBPART B

Organization and Personnel

820.20 Organization

1. Q. The GMP states that "where possible" the quality assurance program should be independent of the manufacturing operation. How does an investigator determine whether such separation is possible?

   A. The preamble to the GMP final rule provides some assistance for making this decision. Comment 30 (pg. 31515 of the July 21, 1978 Federal Register) states the requirement that "each manufacturer prepare and implement quality assurance procedures to assure that a formally established and documented quality assurance program is performed," but this requirement does not necessarily "mandate that each manufacturer have a separate quality assurance unit." The Agency stresses the need for an "objective and accountable quality assurance process," but

does not dictate specific organizational requirements to achieve this goal. "FDA is more interested in the adequacy and appropriateness of the quality assurance program that each manufacturer has developed than in the organizational structure of the company."

Basically, the decision on whether the two functions ought to be kept independent will be governed by the firm's size and the number of properly trained personnel available for quality assurance activities. Usually, small firms do not find it possible to keep these functions independent. Typically, investigators will find an individual performing several functions, such as packaging, labeling, quality assurance, storage, etc. If investigation indicates that the quality assurance program is functioning effectively, the fact that the firm does not have an independent QA program need not necessarily be considered a significant deviation. Whether to list this on the 483 is left to the judgement of the investigator.

2. Q. What constitutes a documented quality assurance program, as required by 820.20?

A. Basically, documentation consists of written inspection, test, and calibration procedures, etc. necessary to perform the activities specified in 820.20(a), Quality assurance program requirements, and in other applicable parts of the GMP. Large firms may have a quality assurance or quality control manual in which they maintain

documents relating to quality assurance, such as descriptions of the QA program's organization, functions, assignment of specific responsibilities and authorities, and other information. In very small firms, the documentation may consist merely of inspection and test procedures or protocols, an audit procedure checklist, calibration and maintenance procedures, etc.

820.20(a) Quality assurance program requirements

1. Q. 820.20(a)(1) through (4) contains four areas of requirements for a manufacturer's quality assurance program. Are these the only areas the quality assurance program should cover?

   A. No. The quality assurance program should cover all activities necessary to assure quality in the product and in the manufacturing process. Manufacturers design QA programs to fit product and process specifications. At a minimum, quality assurance programs must assure that all applicable parts of the GMP are properly implemented and met.

2. Q. 820.20(a)(2) requires that the quality assurance program assure, among other things, that manufacturing materials are approved or rejected. Does this mean that the manufacturer must inspect manufacturing materials at incoming?

A. Under 820.20(a) Quality Assurance is responsible for defining inspection criteria and for accepting or rejecting manufacturing materials. Normally, acceptance of manufacturing materials is handled in the same manner as incoming components. This might include testing of the manufacturing materials by the materials supplier with the manufacturer receiving a protocol of assay or copy of testing results. It is left to the manufacturer's discretion to decide if materials should be tested for conformance to specifications or if acceptance of the supplier's certification would be sufficient. At a minimum, manufacturing materials to be used in producing the device should be visually examined prior to use for evidence of damage and to make certain the materials are what was ordered. This does not necessarily mean that examination must take place at the time such materials come in, unless they are intended for immediate use.

820.20(b) Audit Procedure

1. Q. Suppose a manufacturing operation consists of fewer than 10 people. An audit is being conducted by the managers, who are directly involved in assembling and testing the device. Does such a firm comply with the independent auditor requirement of 820.20(b)?

A. Although an independent audit is preferred, FDA places more emphasis on the training and qualifications of auditors than on their independence from the subject area of the audit. If a very small firm — particularly one in which everybody is directly involved in daily production activities — concludes that an independent audit would be unduly burdensome or impractical, the firm may perform its own audit, provided that it does so according to a written audit plan, such as a list of the areas to be audited and the aspects to be checked, and implements the plan according to a schedule. For each audit, a record must be made of the findings and of any corrections made. Investigators should review a company's audit plans. As a matter of administrative policy, FDA will not seek access to actual internal audit reports during routine GMP inspections. Investigators should not request copies of internal audit reports. The acceptability of self-audit should be judged on a case-by-case basis. The BMD/GMP section may be consulted for guidance (427-7194).

2. Q. Situation: a manufacturer is sampling a device from the assembly line and examining it for workmanship and conformance to specifications. This is done in addition to finished product inspections and testing. Is this adequate to satisfy the GMP quality audit requirement?

A No, this is not a system audit, as specified in the GMP. Section 820.20(b) Audit

Procedures states that planned and periodic audits of the quality assurance program shall be implemented to verify compliance with quality assurance program requirements. The quality audit is an audit of the overall QA system. At a minimum, it should cover all applicable operations, documentation, etc., implemented to (a) meet the quality assurance specifications and procedures listed in the device master record and (b) satisfy requirements of the GMP regulation applicable to the company's quality assurance program. A company's internal audit assesses the adequacy of the QA program and the company's adherence to it.

3. Q. 820.20(b) states that audits shall be performed by appropriately trained individuals. What type of training would be acceptable?

A. Auditors should be sufficiently trained to detect variations and problems in all aspects of the QA program. In order to evaluate findings effectively, report them, and make adequate recommendations, auditors must have a working knowledge of how the device is made (specific procedures to be audited, limitations of the manufacturing process itself, etc.) and of the broader quality assurance principles that apply. Such training may be obtained on the job, through formal classes, or a combination of both. In accordance with 820.25(a), training should be documented. Adequate documentation may take a number

of forms, such as certification, personnel record entry, program agenda, or testing results.

4. Q. When and how should investigators proceed in requesting written certification of internal audits, as required by 820.20(b)?

A. In cases where investigators find there is a question as to whether adequate audits are in fact being conducted, they should consult with the BMD Case Management Branch, HFK-114 (427-8110) prior to requesting audit certification. It is BMD policy not to request written certification on a routine basis.

820.25(a) Personnel training

1. Q. 820.25(a) states that personnel training programs should be documented. What constitutes acceptable documentation?

A. 820.25(a) states "...where training programs are necessary...such programs shall be conducted and documented..." Programs may consist of on-the-job training or formal classes. The manufacturer is allowed discretion in determining the need for a formal training program. Documentation may consist of written instructional

material, tests, certification, or even an indication in a personnel file that training was completed. If a manufacturer has determined that no training program is necessary, investigators should look for instances of deficiencies that would indicate a need for further training in specific areas or techniques: e.g., soldering, welding, desoldering, aseptic handling, sterilization of media, handling of biohazardous materials, etc.

SUBPART D

Equipment

820.60 Equipment

1. Q. A firm manufactures packaging for its noncritical, nonsterile medical devices and treats the parts of the packaging as purchased parts (i.e., incoming inspection, recordkeeping, etc.), but it does not have maintenance schedules for the equipment (machine tools) used in fabricating the packaging components. Should the firm be in compliance with the equipment portion of the GMPs?

   A. Maintenance (lubrication, cleaning, etc.) of machine tools is significant only in situations where the absence of such procedures can affect packaging product specifications. For example, where lack of lubrication in a press, lathe or grinder could cause differences in the dimensions or other specifications of packaging or in the device or its components, written schedules are necessary. Otherwise, they are not required by the GMP.

820.61 Measurement equipment

1. Q. A manufacturer has measurement equipment calibrated by an outside laboratory. If the lab provides certification that calibration was conducted and that standards traceable to NBS were used, would that be adequate?

   A. Yes. The manufacturer, however, should receive data attesting to the accuracy of the measurement equipment before and after calibration and to the conditions under which it was calibrated. The device manufacturer should be notified if equipment is found to be out of calibration when received by the calibration lab so that appropriate remedial action can be taken, if necessary (e.g., retesting of product, recall, calibration schedule adjustments, etc.). Since the lab becomes an extension of the manufacturer's quality assurance program, procedures used by the laboratory should be audited, if possible, as part of the manufacturer's quality audit activity. The equipment user should maintain calibration records and schedule.

2. Q. What does "limits for accuracy and precision" mean in 820.61(a)?

   A. Many manufacturers assume the terms are synonymous, but they are not. Accuracy refers to how closely the mean value in a series of replicate measurements apprcaches

the true value. Precision refers to how closely the values within the series agree with each other. If test results are to be reliable, the tolerances for these terms must be specified.

3. Q. Section 820.61(a) requires that provisions be made for remedial action when accuracy and precision limits are not met. Does this mean that provisions should be made to recalibrate the equipment?

A. Yes, but other remedial action may also be necessary. When measurement equipment is found to have varied outside its accuracy limits, manufacturers are required to repair, replace or (re)calibrate the equipment prior to future use. Further, they must determine the effects that the inaccurate measurements have had on products, and take necessary measures to correct all non-conforming devices on the premises or in commercial distribution.

SUBPART E

Control of Components

§20.80 Components

1. Q. Can a firm be in compliance with the GMP if it accepts components and materials on the basis of a Certificate of Conformance (or Compliance) in lieu of inspection and testing?

A. Yes. If the manufacturer knows the circumstances under which the certificate was generated and it accurately reflects that the components or materials were inspected and tested. The supplier must have specifications that properly define the manufacturer's acceptable limits of the component or material values and should provide test or analytical data with each lot. The data should contain the signature of a responsible individual and be dated. Upon receipt of the components, the firm must check this data against specifications.

Procedures to be followed should be part of the acceptance procedure required by 820.80(a). Where possible and appropriate, an audit of the supplier's procedures should be included as part of the manufacturer's quality audit to ensure that adequate inspections and tests are properly conducted by the supplier.

2. Q. Situation: reserve samples are not maintained by a manufacturer. The manufacturer claims that reserve samples of raw materials are maintained by the supplier. Is this adequate?

A. The GMP does not impose a general reserve sampling requirement, as indicated by comment 76, page 31519, in the preamble to the final rule. For critical devices, it is left to the discretion of the manufacturer to determine if it would be beneficial to retain reserve samples. However, manufacturers of critical devices who decide that sample retention is unnecessary must be prepared to provide an adequate rationale for that decision.

3. Q. Example: a manufacturer of noncritical medical devices performs only a visual inspection of electrical components. A finished device test is conducted, at which time the components are electrically tested as part of the finished device. Is this adequate?

A. Such testing is acceptable in cases where a manufacturer determines that it is necessary and appropriate. A manufacturer must be prepared to demonstrate that component performance can be adequately verified by testing at the finished device level.

Section 820.80(a) states, in part, "...Where deviations from component specifications could result in the device being unfit for its intended use, components shall be inspected, sampled, and tested for conformance to specifications." This requirement, which applies to noncritical components in both critical and noncritical devices, allows a manufacturer to decide which noncritical components should be sampled and tested.

The intent of this requirement was to allow each manufacturer to decide, by evaluating the effects of variations in component performance on the performance of the finished device, which noncritical components need to be tested individually.

Investigators should not arbitrarily conclude that a manufacturer must test all non-critical components on an individual or lot basis. When an investigator believes certain components should be tested before being incorporated into the device, the manufacturer's rationale for not testing these components should be obtained and reported, together with the investigator's rationale on the need for testing and any other pertinent information on the performance history of the components.

4. Q. Some manufacturers of noncritical devices are applying the GMP component requirements at the assembly level. They do not test components until they are incorporated into assemblies, and then test them as part of the assembly. Is this acceptable?

   A. Yes. Although the component requirements were meant to refer primarily to individual components and materials, they may also be applied to assemblies. According to section 820.3(c), "component" means any material, substance, piece, part, or assembly used during device manufacture which is intended to be included in the finished device. Therefore, an assembly can be a component and manufacturers may apply the GMP requirements to assemblies as though they were components. This is especially applicable when assemblies are purchased. The finished device manufacturer is responsible for assuring that all materials and parts used in the assembly are appropriate and adequate for the purpose chosen.

5. Q. What is the policy concerning component traceability?

   A. Traceability is required for critical devices and critical components. Traceability for in vitro diagnostic products is required by the labeling regulation in section 809.10. Traceability is not mandatory for non-critical components and devices (except for in vitro diagnostic devices).

820.81 Critical device, components

1. Q. What should appear on the FD 483 when a firm manufacturing a critical device has not attempted to identify critical components?

   A. If there has been no review of the design for this purpose, cite the firm for failure to evaluate the device for the purpose of identifying critical components. Mark the checklist responses re: critical components as "A." All manufacturers of critical devices must evaluate their designs and identify components that meet the critical component definition given in 820.3(e). FDA recommends a documented protocol or procedure to assure that this determination is logical and consistent with the design basis of the device.

   Investigators who disagree with a manufacturer's selection or nonselection of critical components should indicate the disagreement and the reasons for it in the EIR.

SUBPART F

Production and Process Controls

820.100 Manufacturing specifications and processes

1. Q. Are engineering drawings an adequate alternative to written manufacturing procedures, when required by the GMP?

   A. Yes, in some cases. Written manufacturing procedures are required, as specified by the GMP, to the degree the manufacturer deems necessary for ensuring that finished products meet the approved design. Drawings (e.g., assembly diagrams) can provide instructions such as parts identification, configuration, and assembly instructions. If personnel are sufficiently trained to read and interpret such drawings, the drawings would be acceptable alternatives to written procedures. If, however, data is obtained that indicates mistakes or poor assembly practices, or

if above-normal rejection rates are occurring because of the inadequacy or absence of written instructions, it may be necessary to have written instructions accompany the drawings.

2. Q. Can 820.100(b)(2) be applied to an inadequately controlled ETO sterilization process?

A. Yes, after the sterilization process is established. All processing control operations must be conducted in a manner designed to assure that the device conforms to applicable specifications. Typical controls would include monitoring temperature, vacuum, pressure, sterility testing, etc. and appropriate record-keeping.

3. Q. Section 820.100(a)(2) states that specification changes shall include the approval date and the date the change becomes effective. Does the effective date have to be a specific date? If the manufacturer cannot identify a specific date, can it be omitted?

A. First, an accurate history of changes must be maintained. If the change affects performance, safety, or effectiveness of the device, the specific date on which the change is to be incorporated and, if possible, the lot number, serial number, or other identification of the first units subject to the change should be recorded.

Many firms use terms such as: "When existing stock is exhausted" or "Initiate by..." a certain date. These would be acceptable effective dates for changes that have no impact on device safety or performance. The place provided by the manufacturer on the change record for recording an effective date should not be left blank.

4. Q. Section 820.100(a) states that "(1) Procedures for specification control measures shall be established to assure that the design basis for the device, components, and packaging is correctly translated into approved specifications." What does this mean?

A. After the device, components, and packaging designs are established and qualified, details of the designs must be properly translated into written specifications. Section 820.100(a) requires that controls be provided to assure that the specifications properly reflect the design.

This control of initial specifications and subsequent changes is usually achieved by a detailed review and approval process. To obtain approval of new specifications, many manufacturers use the same procedure and forms used to review and approve changes in drawings or other documentation. The form used — sometimes called

an engineering change notice, drawing change request, etc. -- is reviewed, approved and released by designated individuals. The completed forms become the records which document any changes and their approvals. After the change is made, the changed or new specification is routed for use. This process should also include the systematic collection and filing or disposal of all old, outdated copies of specifications, procedures and drawings. If filed, such documents should be marked "Obsolete."

820.101 Critical devices, manufacturing specifications, and processes

1. Q. Can electrical tests be considered critical operations?

   A. Yes, if a manufacturer so determines. A critical operation, as defined in 820.3(g), means any operation in the manufacture of a critical device that can cause it to fail or to affect its safety or effectiveness. Because electrical tests are used to detect unsafe or ineffective devices or components, they could be considered critical operations. It is the manufacturer who must identify critical operations but the manufacturer's selection and rationale are subject to FDA review.

2. Q. If a firm conducts and records a pressure check on tubing, is a subsequent check of the record sufficient for verification to meet 820.101(a)? (The firm conducts thousands of such checks and has identified them as critical operations.)

A. Yes. A check of the record of the data would be sufficient, provided that QA periodically assures that the pressure check is being done properly and that employees are following established procedure.

820.115 Reprocessing of devices or components

1. Q. The GMP Compliance Program 7878.003, page 5, states that "reprocessing does not include repair or reconditioning of devices that have been returned to the plant." Would this also be true for devices which have been sent out on consignment, i.e., on a trial basis, and returned?

A. Yes. Once the device is finished and shipped, the reprocessing requirements do not apply. If there was a malfunction or defect in the returned product, the failure investigation requirements (820.162) would apply.

2. Q. If a medical device manufacturer no longer makes a product but is still in business to service and repair the particular device, do the GMPs still apply?

A. No. The GMPs do not apply unless the repair service is modifying the device so that it varies from the original specifications, in which case it is considered manufacturing activity and subject to the GMPs.

3. Q. Situation: During the manufacturing process, defective discrete packaged components (ICs, diodes, etc.) are replaced. Under the GMP, would this be considered reprocessing?

A. Yes. Replacement of electronic discrete components in a finished subassembly, component, or device is considered reprocessing since the finished item is recycled through part of the production cycle.

The GMP reprocessing requirements apply to all finished units (materials, subassemblies, discrete components, and finished devices) that are rejected during inspection and later reprocessed through all or part of the production cycle.

In each instance, however, investigators should apply the following criterion: the extent and types of controls necessary for reprocessing

depend on the effect that initial or repeated reprocessing could reasonably be expected to have on the reprocessed unit.

4. Q. In cases involving reprocessing, what does the GMP require by way of the extent and types of controls to be exercised over such operations?

A. The GMP requirements were devised to assure that reprocessed units meet the original or subsequently modified and approved specifications after reprocessing.

Specifications for reprocessing should document the specific tests and processes to be repeated for each replaced component and the limits on the amount of reprocessing permitted for a unit. These specifications should be based on studies to measure the effects of reprocessing operations. For example, if a component is repeatedly replaced, the effect of repeated application of heat during soldering must be determined. If there is an effect such as separation of pad/conductors or degradation of insulation, limits should be set on the number of times a component can be replaced.

On the other hand, replacing a defective printed circuit board (PCB) with a good one may only require marking it defective, segregating it, and, after replacement, retesting the finished device. Procedures used in controlling such reprocessing need only be as detailed as deemed necessary to assure the

finished device or component meets the approved specifications. For noncritical devices, it is left to the manufacturer to decide which controls are necessary to assure compliance with specifications. Regardless of the decisions made, each manufacturer should be prepared to provide rationale for the decision.

SUBPART G

Packaging and Labeling Control

820.120 Device labeling

1. Q. Does failure to meet the GMP requirements for labeling result in a device that is misbranded?

   A. Sometimes. The GMP, however, addresses only the handling and control of labeling, not its contents. When a device is manufactured under conditions that do not meet the GMP labeling requirements, it is considered adulterated. In some cases, failure to comply with the GMP requirements (e.g., failure to proofread) could also result in labeling containing printing errors. In these instances, the devices would also be misbranded.

820.121 Critical devices, device labeling

1. Q. Section 820.121(a) requires labels issued for critical devices to contain a control number. Is this a control number for the labeling, or does it refer to the control number of the finished device?

   A. It is the control number of the finished device, as stated in the second paragraph of comment 106 in the preamble to the GMP, page 31521. However, most labels will also have a drawing or reorder number.

2. Q. The manufacturer of a critical device packs individually packaged and labeled devices into shipping cartons for distribution to hospitals. Each shipping carton contains a number of individual packages. Only the label on the shipping carton contains a control number. Should the packages inside the shipping carton contain control numbers?

   A. Yes. The labels attached to the individual packages should contain control numbers. Section 820.181(a) states that labels issued for critical devices shall contain a control number. Shipping cartons are usually disposed of after being unpacked. If control numbers were not contained on the labels of individual packages, traceability would be lost after the devices were removed from the shipping carton and placed into storage.

SUBPART H

Holding, Distribution, and Installation

820.150 Distribution

1. Q. Can the GMP be used as authority to obtain shipping records for noncritical devices?

   A. No. The GMP does not require noncritical device manufacturers to maintain distribution records. However, the quantity released, date of manufacture, quantity manufactured, and any control numbers used must be contained in the history record.

SUBPART I

Device Evaluation

820.160 Failure investigation

1. Q. Parts 820.162, Failure investigation, and 820.198(b), Complaint files, appear to be the same requirement. Which should I use in a situation where the firm did not do a failure analysis?

   A. Use either one or both, depending on the individual facts of the case. Part 820.162 specifically addresses investigation of failures to meet performance specifications. Part 820.198(b) expands on this and is oriented more toward investigation of user complaints to determine if, in fact, there has been a failure; its effects; and whether the fault lies with the device, the packaging, the labeling or the user.

SUBPART J

Records

820.180 General requirements

1. Q. Is it acceptable for a manufacturer to maintain records on microfilm and dispose the original hard copies?

A. Yes. The utilization of microfiche and/or microfilm reductions in lieu of original record retention is acceptable provided the following conditions are met:

a) All reductions must be readily available at any reasonable time.

b) All necessary equipment must be provided for viewing and copying the records.

c) Reproductions must be true and accurate copies of the original record. Thus,

where the reproduction process results in a copy that does not reveal changes, or additions to the original record, the original must be retained. In this situation, the reproduced copy and any image shown on a viewing screen must note any alteration from the original and indicate that the original record is available.

2. Q. A firm manufactures long-life products such as stretchers. What is the policy regarding retention of records (820.180(b)) for such products?

   A. According to 820.180(b), records must be maintained for a period of time equivalent to the design and expected life of the device, but in no case for less than two years. In some cases, where maintaining records for the life of the device may be overly burdensome or impractical, manufacturers may decide the appropriate time to retain records beyond the two-year minimum. A firm must be prepared to provide a rationale for its decision to discontinue recordkeeping. For example, the decision could be based on the length of time beyond two years that records have been maintained and on the fact that there has been no adverse feedback from customers during that period on the device's "fitness for use."

3. Q. Does the FDA have access to records of repairs conducted by a repair facility?

A. Not under the GMP. Firms that only repair devices are not subject to the GMPs, and, therefore, FDA does not routinely have access to their records. In cases where manufacturers have their own repair facilities, periodic review of the repair records should be part of the manufacturer's effort to identify quality assurance problems. This activity is required by Section 820.20(a)(3) of the GMP.

820.181 Device master record

1. Q. All parts of the device master record appear to exist, but they are maintained at different locations in the plant. Is this adequate?

A. Yes, if there is an accessible list of the documents indicating where the records can be located. The device master record must be a single source document or file, as stated in the preamble to the GMP (Federal Register, page 31523, comment 126). A device master record may exist as: (1) one or more files or volumes of the actual records containing the information required by the GMPs; or (2) a list of such documents and their location, or (3) any combination of the preceding two. These documents, signed, dated, and certified as accurate and up-to-date, must contain the required information, reflect the latest revisions, and be signed and dated to show

they have been checked for accuracy and approval. If the master record contains a list of documentation, the actual documents must be available for inspection at the manufacturing site or other reasonably accessible location.

A device master record provides the means by which a manufacturer can control the configuration of the product design, components, equipment, processes, quality assurance requirements, packaging, and labeling.

Basically, a manufacturer demonstrates compliance with GMP master device record requirements by producing a master document that shows: (1) the identity and location of all GMP-required documentation, (2) formal control and approval of all such documentation, and (3) an adequate description of product, packaging, labeling and system used to produce the finished device.

2. Q. Most manufacturers have some documentation that could be viewed as elements of a device master record. At what point, however, should a master record be considered "Absent," rather than "Deficient?"

A. If a manufacturer has made no attempt to formulate a device master record in accordance with the GMP requirements, the Quality Audit Worksheet elements for

the device master record may be checked "Absent." However, the actual conditions (i.e., whatever documentation does exist) should be explained. If a manufacturer can document the attempt to develop a device master record but has failed to meet some or all of the GMP requirements, the worksheet should be checked:

a) "Deficient" in specific areas that are deficient,

b) "Absent" in those areas where the attempt failed, and

c) "NDN" where the requirement was adequately fulfilled.

In all cases where approved documentation is present and it adequately represents and describes a specific entity for which the GMP requires documentation (i.e., the device, components, process, etc.), the part of the checklist referring to that particular requirement should be marked "NDN."

3. Q. A manufacturer has received complaints of production contamination caused by particulates. The production environment is well controlled and particle counts are acceptable. The particulates appear to be introduced by means of the packaging and gloves worn by the employees. The purchase specifications for these items do not specify particulate control. What GMP deficiencies could the investigator cite?

A. If particulates are a concern, the final inspection procedure should contain a requirement to check for particulates (sections 820.160 and 820.20(a)(4)).

If incoming packaging and gloves are not inspected for particulates, 820.20(a)(4) and (a)(2) could be charged. Failure to include particle limitations in specifications would be an 820.100 charge. If the problem is known and little or nothing has been done to correct the situation, the FD 483 could cite 820.20(a)(3) or, if circumstances should indicate it, 820.198.

4. Q. Are supplier component specifications adequate to meet the master record requirements for component specifications?

   A. Yes, if they accurately reflect the parameter or composition and configuration required for the component to perform the function for which it was selected. Supplier specifications are usually adequate for standard components. A manufacturer who relies on supplier specifications usually has no control over changes made in these specifications and, therefore, must assure at an appropriate point in the manufacturing process that the components received meet the desired specifications.

5. Q. Is a manufacturer allowed to change a component, device, or process and, at a later date, make the necessary changes in the appropriate master record documents?

   A. Yes. There may be instances where it is necessary for a manufacturer to make changes during ongoing production prior to

processing and receiving final approval for the change in the master record. If this is necessary, the changes made and the device(s) affected by the changes must be recorded and the records dated and signed by a responsible individual. These changes, however, must be approved and documented in the master record according to the firm's standard operating procedure prior to distribution of the modified device(s). The manufacturer may destroy temporary records of change when all significant information about the change is recorded in the master record.

820.184 Device history record

1. Q. The history record requirements state that a device history record must be maintained to demonstrate that the device is manufactured in accordance with the master record. What information should the history record contain for a noncritical device?

A. Basically, the history record should show that all necessary operations shown in the master record have been accomplished. For example, all inspections and test results called for by the master record should be made a part of the history record. In addition, it should record the dates of manufacture, the quantity manufactured,

the quantity released for distribution, and any control numbers used There is no mandatory requirement for control numbers for noncritical devices except in the case of in vitro diagnostic products. A record of labeling examination made prior to issuing labels for use must be part of the history record (820.120(e)). Any reprocessing should also be part of the record.

2. Q. History records are maintained by a noncritical device manufacturer, but they are not together in a file or referenced on a single document. Does this arrangement meet the GMP requirement?

A. There are no specific requirements in the GMP that device history records be maintained as a single document or file. However, Section 820.20(a)(1) requires that the quality assurance program assure review of production records. Device histories must, therefore, be maintained in a form that will facilitate timely review prior to release of the product.

For critical devices, a history record is required for each control number. One or more designated individuals must assure that all GMP-required records and documentation are present and complete. The record must also establish that the release of the device was consistent with the release criteria.

The foregoing also holds true for in vitro diagnostics, for which traceability must be maintained in all cases.

Typically, these requirements are most conveniently or effectively met by use of a single history record or file.

820.198 Complaint files

1. Q. What is the definition of a complaint?

   A. As stated in 820.198(a), a complaint, written and/or oral, is an expression of dissatisfaction regarding identity, quality, durability, reliability, safety, effectiveness and/or performance of a device.

2. Q. Situation: access to complaints has been refused, except for those chosen by the manufacturer. Does the FDA have access to all complaints?

   A. FDA has clear authority under section 704(e) of the Act to inspect and copy all records required under section 519 or 520(g). Since the GMPs were promulgated under the authority of Sections 519 and 520(g), the regulation provides FDA with authority to inspect, review and copy any complaints on devices manufactured on or after 12/18/78 (the effective date of the GMP). When requesting to review complaints, the investigator should be as specific as possible about such things as the device in question, the period of time covered, etc.

3. Q. A manufacturer claims no complaints have ever been received and, therefore, has made no provision for maintaining a complaint file. Is this a GMP deviation?

A. Yes. All manufacturers are required to make provision for receiving, reviewing, and investigating complaints; to establish how these activities are to be performed; and to designate someone to perform them. Such preparations must be made regardless of whether or not complaints have been received. If manufacturers cannot show they have done so, this absence should be listed on the FD 483.

4. Q. Does the GMP require manufacturers to provide written procedures for processing complaints?

A. No, there is no specific requirement in Section 820.198 for written procedures. However, the need for written procedures must be decided on a case-by-case basis. At a given manufacturing facility, the determination of procedures needed for processing complaints should be made on the same basis as written procedures needed for any other operation. Written procedures are usually provided to facilitate communication and consistency. GMP requirements for complaints are extensive

and normally would require a written protocol or procedure specifying authority, responsibilities, and the process to follow in receiving, reviewing and investigating complaints.

In very small firms, where division of work is minimal and authority and responsibilities are obvious, an investigator should be guided by the circumstances. In some cases, the GMP requirements themselves may be sufficient as a protocol for handling complaints.

5. Q. Should requests for repairs be included in the complaint file?

A. No. Repairs that can be characterized as routine service need not be included in the complaint files. Any correspondence or record indicating customer dissatisfaction, however, should be considered a complaint, as defined by 820.198(a). In reviewing service requests, manufacturers should have an SOP for identifying complaints. In some cases, the product warranty can be used as a measure to decide if repairs should be considered routine. An excessive number of service requests within the warranty period should require appropriate review and analysis of service data as part of the "identifying" of quality assurance problems in 820.20(a)(3). Manufacturers should maintain records of repairs and include the repair data when calculating reliability.

6. Q. Situation: complaints are filed and reviewed at the manufacturer's home office, where the quality assurance group is located. Is this adequate?

A. Yes, but copies of the followup investigations of complaints must be transmitted to, and maintained at, the actual manufacturing establishment in a file designated for device complaints (820.198(d)).

GENERAL QUESTIONS

Critical Devices

1. Q. Can a Class II device be classified as a critical device?

   A. Yes. Classification of a device, however, is not in itself a guide to its criticality. Both Class II and III devices are on the guideline list of critical devices. There are some Class III devices that are not critical devices. The selection of devices as critical is independent of the device classification process (Classes I, II or III). A device must meet the critical device definition before it is considered a critical device. Before FDA adds a device to the critical device list, it must consult with the device GMP Advisory Committee. A device is officially added to the critical list only after formal publication to that effect appears in the Federal Register.

2. Q. Are line-powered defibrillators critical devices? The GMP list contains only DC-powered defibrillators.

A. Yes. Line-powered defibrillators are also critical devices. Item 28 on the critical device list, "Defibrillator, DC-Powered," includes line-powered defibrillators. The DC connotation refers to the capacitor discharge output, which is used in both battery-powered (DC) and line-powered (AC) units.

3. Q. Are hemodialysis solutions considered critical devices?

A. Yes. Hemodialysis solutions are part of Item 36, "Hemodialysis Systems," in the list of critical devices contained in the GMP preamble (pg. 31512, Federal Register, July 21, 1978). Peritoneal dialysis solutions are presently considered to be drugs.

Do the GMPs apply?

1. Q. Firm A prepares specifications and standard operating procedures; it also orders, inspects, and tests parts and materials. These are provided to Firm B, which fabricates, assembles, packages, and labels the device with Firm A's label and ships the product to Firm A's warehouse for distribution. Is Firm A subject to the GMP?

A. Yes. It is Firm A's general responsibility to assure that the device is manufactured according to the GMP and that it is safe and effective. Further, Firm A is specifically responsible for any of its activities that are subject to GMP requirements (i.e., SOPs, specifications and acceptance of components). Since the product bears its label, Firm A would normally receive complaints and be required to process them.

2. Q. Are manufacturers subject to the GMP who produce devices for export only?

A. No. Devices for export only are not adulterated or misbranded if they meet the requirements of 801(d) of the Act. Even though these requirements do not specifically provide exemption from the GMP, such devices would be exempt from the penalties of not meeting the GMP. Manufacturers of devices for export only are not routinely scheduled for GMP inspections.

3. Q. How should the GMP be applied to a repacker/relabeler?

A. According to 820.3(k), repackers and/or relabelers are manufacturers. They are subject, therefore, to all GMP requirements applicable to repacking/relabeling activities that are being, or should be, conducted.

In a situation where the device is actually manufactured by a contract manufacturer and supplied to the repacker/relabeler in primary packaging, GMP responsibilities would be divided. To assure the device was received undamaged, the repacker/relabeler would be responsible for conducting a visual inspection and for meeting other applicable requirements in such areas as final packaging, labeling, distribution, complaint processing, failure investigation, organization, personnel, buildings, etc. The contractor would be responsible for many of the same requirements and for others, as they apply, in accordance with agreements previously established between the two parties. For example, the responsibility for developing and controlling changes to specifications may belong to either party. Although the master record may be developed and controlled by either party, it must be available to the contractor. The master record or an accurate, approved copy must be located at the actual manufacturing site.

The party whose name appears on the labeling has general responsibility for assuring that the device is manufactured according to the GMP and is safe and effective. Depending on the individual circumstances, either or both parties may be held responsible by FDA for an ineffective or defective device.

4. Q. A critical device manufacturer provides replacement components to users of his device. Do the GMPs apply to this activity? Should traceability be maintained?

A. No, assuming the component in question is not considered a finished device (See Question 5). Once the device is distributed, the GMP does not apply except for complaint and failure investigation. There is no GMP requirement that traceability be maintained on a replacement component for a device already distributed.

5. Q. A subsidiary of a hemodialysis system manufacturer manufactures a blood leak detector for use in the parent firm's hemodialysis system. Some of the blood leak detectors are incorporated into, and sold as part of, the hemodialysis system. Others are sold directly to owners of the systems as additions to the existing system, or as replacement units. Is a subsidiary manufacturer of the blood leak detector a component or a finished device manufacturer?

A. The blood leak detector manufacturer is a finished device manufacturer. This conclusion is based on the fact that the device is sold to users to enhance the function of the hemodialysis system. Since the hemodialysis machines are capable of operation without these devices and since they are marketed separately for use with the hemodialysis system, they are considered to be accessories - and, hence, finished devices - for purposes of applying the GMP.

6. Q. A suture manufacturer, who also extrudes the strands of fibers to be assembled into sutures, claims that the extrusion process is a component manufacturing process and not subject to device GMPs. The manufacturing and extrusion of fibers is performed in the same building/facility as the assembly of the finished device. Do the GMPs apply in this situation?

A. In this situation, the manufacture of suture fibers is subject to the applicable parts of the GMP. When a manufacturer fabricates components exclusively for use in a finished device manufactured in the same facility as the components, the finished device manufacturer has full control of the component manufacturing process. In such cases, the manufacture of component parts is considered part of the total production process for the finished device and, therefore, subject to applicable requirements of the GMP.

The agency elected not to require component manufacturers to comply with the GMP because manufacturers of components may supply only a fraction of their production to finished device manufacturers. In addition it was suggested that components for many finished devices are readily available in the marketplace and are not manufactured exclusively for use in devices. None of this rationale applies to the firm in the example under discussion. Furthermore, part 820.1 of the GMP regulation encourages component manufacturers to use the GMP as a guideline, where appropriate.

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